

DRUG NAME: Fulvestrant

SYNONYM(S): ICI-182780; ZD-9238¹

COMMON TRADE NAME(S): FASLODEX®

CLASSIFICATION: hormonal agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Fulvestrant is an estrogen receptor antagonist with no partial agonist effects, including its effects on the uterus. It competitively binds estrogen receptors with an affinity comparable to estradiol. Fulvestrant down-regulates estrogen and progesterone receptors, inhibits the growth of estrogen-sensitive human breast cancer cells within the G1 phase, and suppresses breast tumour growth.^{2,4}

PHARMACOKINETICS:

Distribution	widespread extravascular distribution; steady state within 1 month	
	cross blood brain barrier?	no information found
	volume of distribution	3-5 L/kg
	plasma protein binding	99%
Metabolism	extensively metabolized, primarily in the liver via many biotransformation pathways (e.g., oxidation, hydroxylation, etc.) ^{2,3}	
	active metabolite(s)	yes (unnamed); however, <i>in vivo</i> activity due to parent drug
	inactive metabolite(s)	yes
Excretion	rapidly via hepatobiliary route; exposure and elimination primarily determined by rate of release from injection site	
	urine	<1% (as metabolites)
	feces	90% (as metabolites)
	terminal half life	40 days ³
	clearance	11 mL plasma/min/kg (rate approximates hepatic blood flow)

Adapted from standard reference² unless specified otherwise.

USES:

Primary uses:

*Breast cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to fulvestrant, ethanol, or benzyl alcohol²
- pregnant or breastfeeding women²

Caution:

- **bleeding** and/or **hematoma** may result from IM administration to patients on anticoagulants, with bleeding diatheses, or thrombocytopenia^{2,5}
- **estradiol levels** may be falsely elevated²
- **sciatica, neuralgia, and peripheral neuropathy** are reported secondary to the site of intramuscular injection; if administering at the dorsogluteal site, consider the close proximity to the sciatic nerve and large blood vessels²

Carcinogenicity: In animal studies, an increased incidence of testicular Leydig cell tumours was reported in males dosed at 90% of the systemic exposure achieved in women receiving the recommended therapeutic dose. In 10% of the cases in adult subjects, these tumours were malignant.^{2,6}

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Fulvestrant is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.²

Fertility: In animal studies, fulvestrant affected both female and male fertility. Effects in females were consistent with the antiestrogenic activity of fulvestrant, with a reversible reduction in fertility occurring at 0.6% of the human equivalent dose. Effects in males included spermatozoa loss, seminiferous tubular atrophy, and degenerative changes in the epididymides, occurring at 100% to 400% of the systemic exposure achieved in women receiving therapeutic doses. Effects on the testes and epididymides persisted at 20 weeks post fulvestrant discontinuation.²

Pregnancy: In animal studies, fulvestrant crossed the placenta and exhibited effects on embryo/fetal development consistent with antiestrogenic activity. Reduction in embryonic survival, delayed fetal development (e.g., non-ossification of the first cervical vertebra) and increased incidence of fetal abnormalities (e.g., tarsal flexure, edema, and shortened digits) were observed in animals at doses ranging from 0.6% to 100% of the human equivalent dose.² Contraception is recommended in female patients treated with fulvestrant throughout the treatment period and for one year following the last dose.⁷

Breastfeeding is not recommended due to the potential secretion into breast milk. Animal studies have demonstrated distribution of fulvestrant into milk.³ Women may begin breastfeeding one year after the last dose of fulvestrant.⁷

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important^{8,9}.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/ febrile neutropenia	anemia (4-40%, severe ≤2%) ^{2,5}
	thrombocytopenia (3%, severe <1%) ⁵
cardiac	ischemic cardiovascular disorders (1-2%, severe <1%) ^{2,10}
gastrointestinal	<i>emetogenic potential</i> : minimal ¹¹
	abdominal pain (12-16%) ^{2,5}
	constipation (5-16%) ^{2,5}
	diarrhea (4-25%) ^{2,5}
	nausea (10-28%) ^{2,5}
	vomiting (6-15%) ^{2,5}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
general disorders and administration site conditions	<i>extravasation hazard</i> : none ¹²
	<i>asthenia</i> (5-23%)
	edema, peripheral (7-9%) ^{2,5}
	fatigue (7-32%, severe ≤11%) ^{2,5}
	fever (5-6%) ^{2,5}
	flu syndrome (7%)
	GI disturbances (20%)
	<i>injection site reaction</i> (7-27%, severe <1%) ^{2,3,5,10} ; includes pain, neuralgia, peripheral neuropathy, sciatica ²
non-cardiac chest pain (7%)	
hepatobiliary	<i>hepatic failure</i> (severe <1%); see paragraph following Side Effects table
	hepatic necrosis (severe <1%); see paragraph following Side Effects table
immune system	<i>hypersensitivity reaction</i> (≥10%); see paragraph following Side Effects table
infections and infestations	hepatitis (<1%); see paragraph following Side Effects table
	nasopharyngitis (4-6%)
	pharyngitis (16%)
	urinary tract infection (2-6%, severe <1%) ^{2,10}
investigations	alkaline phosphatase increase (18%); see paragraph following Side Effects table
	<i>ALT increase</i> (5-34%) ^{2,5} ; see paragraph following Side Effects table
	<i>AST increase</i> (5-48%) ^{2,5} ; see paragraph following Side Effects table
	bilirubin increase (≤4%) ^{2,5} ; see paragraph following Side Effects table
	creatinine increase (≤74%) ⁵
	weight loss (2%) ⁵
metabolism and nutrition	anorexia (4-12%) ^{2,5}
musculoskeletal and connective tissue	arthralgia (6-19%, severe 2%) ^{2,10}
	arthritis (3%)
	<i>back pain</i> (7-14%, severe 9%)
	<i>bone pain</i> (5-16%)
	myalgia (7%)
	osteoporosis (<1%)
	pain in extremity (6-7%)
nervous system	anxiety (5%)
	depression (6%)
	dizziness (6-7%) ^{2,5}
	dysgeusia (3%) ⁵
	<i>headache</i> (7-15%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	paresthesia (6%)
psychiatric	insomnia (7%)
reproductive system and breast disorders	pelvic pain (10%)
	vaginal bleeding (<1%) ^{3,5} ; usually within 6 weeks of switching from prior therapy ³
respiratory, thoracic and mediastinal	cough (5-11%) ^{2,5}
	dyspnea (4-15%) ^{2,5}
skin and subcutaneous tissue	alopecia (2-6%) ⁵
	pruritus (6%) ⁵
	rash (4-7%) ^{2,5}
	sweating (5%)
vascular	hot flash/vasodilation (6-18%) ^{2,3}
	hypertension (4-5%)
	thromboembolic events ($\leq 2\%$, severe <1%) ^{2,10,13} ; includes pulmonary embolism ¹³

Adapted from standard reference² unless specified otherwise.

Fulvestrant is associated with **elevated transaminases, bilirubin, and alkaline phosphatase**, which may not be reversible upon discontinuation of treatment. Hepatic failure, hepatic necrosis, and hepatitis have been reported, even in patients without liver metastases. Fulvestrant clearance is decreased in women with moderate hepatic impairment, resulting in a 70% increase in AUC compared to women with normal hepatic function. Monitor for increased side effects in patients with hepatic impairment and avoid using fulvestrant in patients with severe hepatic impairment if possible.²

Hypersensitivity reactions, including angioedema and urticaria, may occur shortly after fulvestrant injection or up to several days later. Localized pruritus and urticaria at the injection site may arise after prior uneventful injections. Reactions may develop over time into a systemic allergic response such as widespread urticaria. Discontinuation of fulvestrant treatment may be required.²

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anastrozole ^{14,15}	anastrozole trough concentration decreased	possibly via upregulation of hepatic metabolic enzymes by fulvestrant or via upregulation of UGT1A4 by 17 β -estradiol metabolite and fulvestrant	none required; clinical significance unknown
estradiol immunoassay (antibody based) ^{2,16}	falsely elevated estradiol levels	structural similarity of fulvestrant and estradiol	consider alternate testing method (e.g., liquid chromatography-mass spectrometry)

Fulvestrant is a minor substrate of CYP 3A4; dosage adjustments are not considered necessary during co-administration with CYP 3A4 inhibitors or inducers.²

SUPPLY AND STORAGE:

Injection: AstraZeneca Canada Inc., Sandoz Canada Inc., and Teva Canada Limited supply fulvestrant as 250 mg/5 mL single-use pre-filled syringes for intramuscular administration. Ethanol and benzyl alcohol are included as inactive ingredients. Refrigerate. Store in original package to protect from light.^{2,17,18}

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in **bold, italics**

Subcutaneous	do NOT use ⁵
Intramuscular^{2,5,17-20}	over 1-2 min (for each injection), into the gluteal muscle For improved patient comfort, ³ solution may be warmed slightly prior to administration by: <ul style="list-style-type: none"> removing the syringe from the fridge up to 1 hour before use, or by rolling the syringe gently between hands prior to injection.
Direct intravenous	do NOT use ⁵
Intermittent infusion	no information found
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	do NOT use ⁵
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in **bold, italics**

Intramuscular: Cycle Length: **4 weeks^{2,19,20}** **Initial** (cycle 1): **500 mg IM for one dose on days 1, 15, and 29**
Maintenance (cycle 2 onwards): **500 mg IM for one dose every 28 days**

Administer as two 250 mg injections, one into each buttock.

Concurrent radiation: no information found

Dosage in renal failure: CrCl > 30 mL/min: no adjustment required²
CrCl ≤ 30 mL/min: no information found

BC Cancer usual dose noted in ***bold, italics***

Cycle Length:

calculated creatinine clearance = $\frac{N \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

- mild impairment (Child Pugh A): no adjustment required; monitor for side effects as clearance may be reduced²
- moderate impairment (Child Pugh B): no adjustment required; monitor for side effects as clearance may be reduced; consider dose reduction to 250 mg^{2,7}
- severe impairment (Child Pugh C): avoid²

Dosage in dialysis:

no information found

Children:

safety and efficacy have not been established

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